The Correlation between Small Placental Volume Measured by Three-dimensional Ultrasonography and Adverse Pregnancy Outcomes: An Observational Study

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ABSTRACT

Objective: The placenta is a vital organ in the growth and development of fetuses within the uterus. The size of the placenta is positively associated with fetal well-being. The aim of this study was to investigate any potential correlation between placental volume and negative pregnancy outcomes.

Materials and Methods: This prospective cohort study was conducted at the department of obstetrics and gynecology, Bhumibol Adulyadej Hospital, Thailand between October 2023 and February 2024. Subjects were singleton pregnant women ever the age of 18 without underlying diseases, namely: diabetes mellitus, hypertension, and autoimmune diseases. Ultrasonography was performed between the gestational ages of 28 and 36 weeks. Placental volume was measured via 3-dimensional ultrasonography and analyzed with maternal and neonatal outcomes.

Results: A total of 132 participants were recruited. The mean age of participants was 28.6 years old. The abnormal (AV) and normal (NV) placental volume groups consisted of 14 and 118 cases, respectively. The AV group was older, with higher parity, cesarean delivery rate, and estimated blood loss. This group's newborns had lower Apgar scores rated at 1 and 5 minutes and more neonatal complications than the NV group (with statistical significance). Maternal age exceeding 34 years could also be used to predict abnormal placental volume with sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) at percentages of 57.1, 81.4, 26.7 and 94.1, respectively.

Conclusion: There is a correlation between placental volume abnormality and certainly adverse outcomes for newborns. Maternal age greater than 34 is associated with higher occurrence of placental volume abnormality.

Keywords: Placental volume; 3DUS; adverse pregnancy outcomes (Siriraj Med J 2024; 76: 595-603)

INTRODUCTION

The placenta is the most important organ of the fetus which undergoes significant changes throughout pregnancy.[1,2] It plays a major role in fetal growth and continuity of pregnancy by ways of nutrients and oxygen transferred through the placental circulation.[3,4] Any impairment in placental development and deficiency of its function can be an important cause of adverse pregnancy and fetal outcomes.[5] Low oxygen concentration in maternal circulation signals for the development of new vessels, and the enlargement of the placenta.[6] Placental growth and development are typically correlated with

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Received 26 May 2024 Revised 16 June 2024 Accepted 30 June 2024
ORCID ID:http://orcid.org/0000-0002-4990-3185
https://doi.org/10.33192/smj.v76i9.269444

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measures such as placental weight and volume. Many factors such as race, smoking, previous medical problems, pre-pregnancy body mass indexes (BMI), and total weight gain were associated with placental volumes.[7] The result of placental weight to newborn's birth weight ratio was defined as placental to birth weight ratio (PFR). It is widely recognized as an important indicator of placental function.[8]

Previous studies found that abnormal placental volume (PV) was linked to adverse pregnancy outcomes (APO) such as preeclampsia with severe features, fetal growth restriction (FGR), preterm delivery, abnormal fetal testing, respiratory distress syndrome, 5-min Apgar < 7, neonatal intensive care unit (NICU) admission, and stillbirth.[9,10] These negative outcomes were more likely in pregnant women with prior medical conditions, namely diabetes mellitus, chronic hypertension, certain infectious diseases, smoke, lower education and socioeconomic status.[11] The placental volume measurements have been incorporated into the assessment of pregnancy risk for APOs to improve specificity of prediction and reduced neonatal morbidity.[9]

Ultrasound is the prevalent imaging modality to study the placenta in clinical settings. It can be provided with low cost and broad availability.[12] There was a report of a weak association between two-dimensional ultrasonography (2DUS) and perinatal outcomes.[13] Quantitative evaluations of three-dimensional ultrasonography (3DUS) were used to evaluate placental volumes.[14] This practice has not yet been incorporated into routine clinical care. These new releases of 3DUS technology have been useful tools for enabling quality imaging to reach the prenatal prediction and future planning for obstetrician to follow antenatal care and for pediatricians to have high awareness of neonatal complications and post-delivery planning for each patient.[15,16]

There were limited reports on whether or not 3DUS placental volumes, in association with neonatal complications, might be used to determine appropriate the risk modification through changes in antenatal care (ANC).[17,18] This study aimed to examine the correlation between placental volume measured by 3DUS and perinatal outcomes in pregnant women who came for routine ultrasound protocol at the gestational age between 28 and 36 weeks. For helping obstetricians and pediatricians to predict the perinatal outcomes and to improve antenatal care.

MATERIALS AND METHODS

This investigation was conducted as a prospective cohort study. The Ethics Committee of Bhumibol Adulyadej Hospital (BAH) institutional review board (IRB72/66) approved the study. The associated registration number can be found on the Thai clinical trial website (www.thaiclinicaltrials.org): TCTR20230908005.

Enrollment

Pregnant women who attended ultrasound sessions at the Department of Obstetrics and Gynecology, BAH, Bangkok Thailand in their third trimester antenatal care between October 2023 and February 2024 were recruited. Inclusion criteria were singleton pregnant women, aged 18 and older, who attended antenatal care at BAH, 28 to 36 weeks of gestation, and no underlying medical conditions, including Human Immunodeficiency Virus (HIV) infection, pregestational hypertension, pregestational diabetes mellitus, and systemic lupus erythematosus (SLE). Exclusion criteria included subjects who received no antenatal care (ANC), inability to communicate in Thai language, and incomplete medical data. All participants received briefings about the investigation and signed the informed consent. Demographic data collected from each participant including maternal age, body mass index (BMI), prior medical conditions (e.g., hypertensive disorders, thalassemia, SLE, pregestational diabetes), parity, gestational weight gain, gestational age at the day of delivery, route of delivery, estimated blood loss, other maternal and neonatal complications. The flow chart of the study is presented in Fig 1.

3DUS measurement

Participants came for their ultrasonography at antenatal care during the third trimester. During the routine ultrasound session for monitoring fetal growth, experienced MFM fellows and obstetric staff also measured placental dimensions using three-dimensional ultrasound probes and recorded images of the placenta. The ultrasound device used in this current study was the Voluson E10 ultrasound machine (GE Healthcare, WI, USA). The three-dimensional probe was equipped with a 4- to 8-MHz transducer. The measurement procedure was done in two steps, to collect placental images and to calculate placental volumes. Inter- and intra-observer agreement were calibrated and reported reliability at level of 0.9 and 0.95, respectively.

We used 2DUS to identify the longest view of the placenta and adjusted the volume box to scan the placental volume.[10] However, the placental images that could not be seen entirely were excluded. The 3D placental sonography was then transferred to a computer graphics program using the ViewPoint 6 (3-dimensional Sonoview, GE Healthcare, WI, USA) configuration program. First,

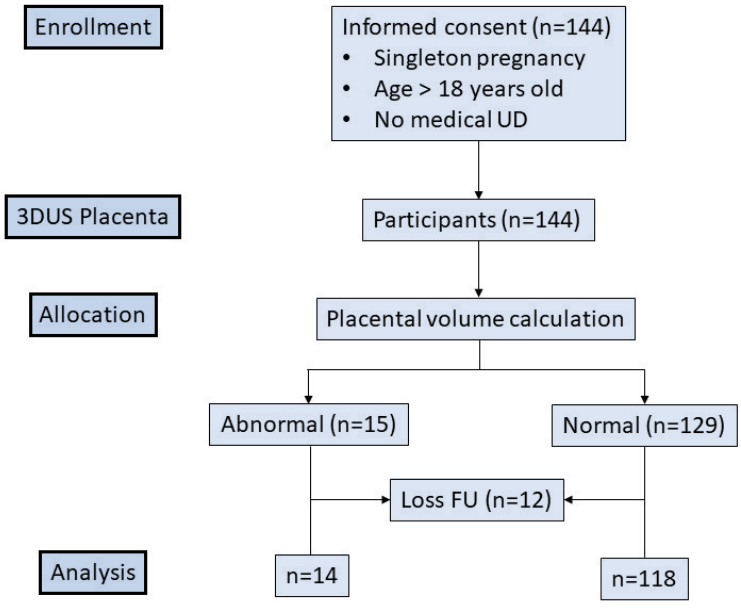


Fig 1. Flow chart of study.
Abbreviations: UD: underlying diseases, 3DUS: 3-dimensional ultrasonography, Abnormal: abnormal placental volume (<10 percentile), Normal: normal placental volume (between 10 and 90 percentile)

the reference image was chosen on the three orthogonal sections on the A plane. Second, the image that we used as a reference, which consists of outlining repeated contours of the placenta, was rotated six times by 30 degrees. These measurements were then analyzed using the VOCAL software (3-dimensional Sonoview; GE Healthcare, WI, USA), employing a rational technique to obtain accurate placental dimensions. After finishing the completed rotation, the total placental volume was automatically calculated as presented in Fig 2. For each participant, the single operator measured the placental dimension two times and the mean volume was calculated. The operator was blinded from the other measurements to ensure unbiased and accurate results. The placental dimension from both sonographs was calculated to placental volume and recorded. Abnormal placental volume was defined

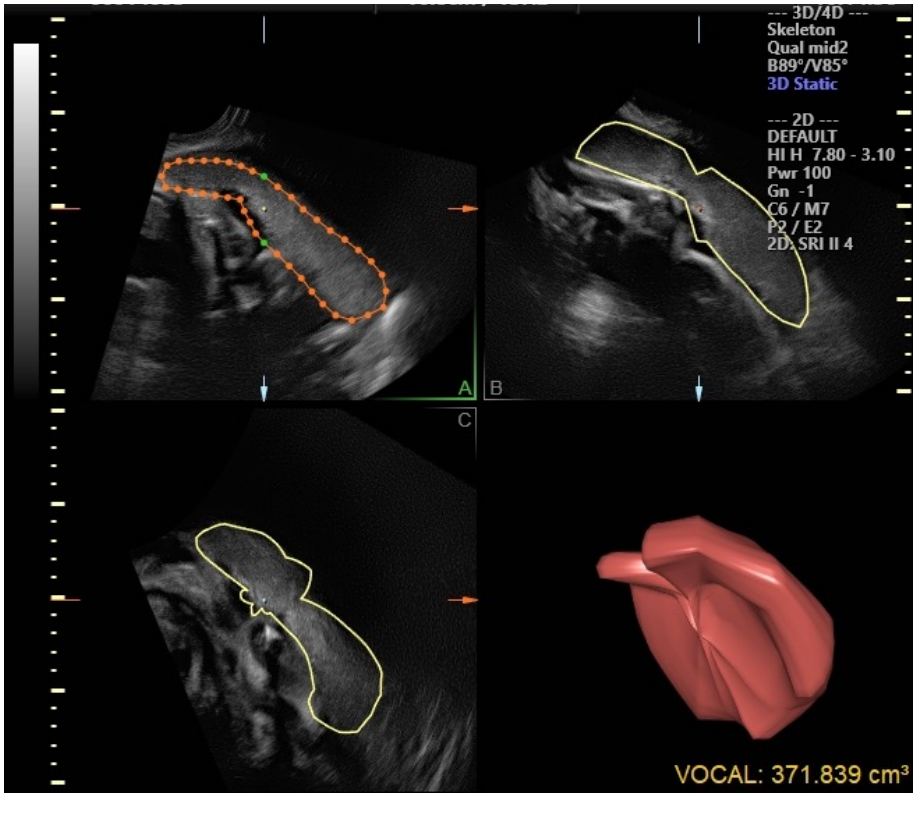


Fig 2. An example of placental volume measurement obtained using the virtual organ computer-aided analysis (VOCAL) method. The rendered image of the volume is shown in the right lower panel.

as the placental volume that less than 10 percentiles of normal range. After all subjects' newborns had been delivered either naturally or by obstetric indication, maternal and neonatal data were collected. It included GA at delivery (in weeks), absolute gestational weight gain, neonatal birth weight and the presence of some complications during maternal intrapartum and adverse perinatal outcomes.

Statistical analysis

The data was processed by using the SPSS version 18.0 (SPSS Inc, Chicago, IL, USA) programs. Continuous and category variables were analyzed and expressed as mean and standard deviation. Independent t-test or Chi-square tests were used for analyzing the category variables. The univariate logistic regression was used to evaluate the correlation between placental volume and clinical factors. Receiver operating characteristic (ROC) curve was used for evaluating the maternal age of the appropriate cut-off point. The correlation between placental volume measured by 3DUS and adverse pregnancy outcomes was considered. A p-value less than 0.05 was classified statistically significant.

RESULTS

A total of 132 participants were recruited during the period of study. There were 14 and 118 cases in abnormal (AV) and normal (NV) placental volume groups, respectively. The AV group refers to a group where members' placental volume was below the 10th percentile for their gestational age at the measured day as assessed by 3DUS.[2]

The mean age of participants was around 28.6 years old. Subjects in the AV group were statistically older than the NV group (32.6 and 28.1 years old). One-third (43/132) of subjects were nulliparous. Most subjects (120/132) delivered at GA for more than 37 weeks. Two-thirds (85/132) gave birth by vaginal delivery. The AV group had higher parity, higher cesarean delivery rate, higher estimated blood loss, babies with lower Apgar scores rated at one and five minutes, and higher neonatal complications than the NV group with statistical significance as shown in Table 1. Both groups had comparable weight gain, pre-pregnancy BMI, maternal consequences, NICU admission, low Apgar score rate, respiratory distress syndrome, fetal growth restriction, and oligohydramnios rate.

The ROC curve of maternal age was generated to predict an abnormal placental volume as shown in Fig 3. It gave sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) at percentages of 57.1, 81.4, 26.7, and 94.1, respectively. For the secondary outcome, the univariate logistical regression and multivariate analysis of abnormal placental volumes and clinical factors (maternal and neonatal) was presented in Table 2. A maternal age exceeding 34 years was the only significant maternal factor for abnormal placental volumes.

According to Table 2, those with a maternal age greater than 34 years old, cesarean delivery, or blood loss of more than 0.5 liters significantly had a 5.82-, 3.79-, and 3.46- times chance of placental volume abnormality versus others in the same categories. Participants below the age of 34 and those with babies with low Apgar score at 1 min with respiratory complications had 9.67- and 65-times higher risk of placental volume abnormality than the control groups respectively. Parity, gestational age at birth, total weight gain, pre-pregnancy BMI, maternal underlying disease, FGR, and NICU admission showed no association with abnormal placental volume.

DISCUSSION

Placental volume indicates intrauterine fetal health.[19] Measurement of placental thickness and calculated volume using 2DUS requires more experienced sonographers. This technology 3DUS has enabled the quantification of placental volume measurement more precisely. The computerized aids helped entirely level sonographers to perform accurate measurements for general obstetrician hands.[13]

The current study was conducted in singleton pregnancy during the early third trimester (28-36 weeks). The previous studies (according to Table 3) of PV measurements were performed during 7 and 14 weeks.[1,3,5,10,11] There were many changes from several factors throughout pregnancy. PV measurements in the first trimester might be too long a waiting period to be used for predicting obstetric outcomes in the next 6 months. For these reasons, we conducted this investigation to evaluate placental volumes at near-term.

Naturally, placental volumes vary by gestational age.[2] Abnormal placental volume in the current study occurred in older participants and had higher parity than those in the normal placental volume group. Around two-thirds of subjects from Reijnders', Soongsatitanon's, González's, and Farina's reports were nulliparous, and the mean maternal age of their study ranged from 30.4 to 32.8 years old. While one-third of Quant's and the present study were nulliparous. The mean age of Quant's and the present study were 31 and 28.6 years old, respectively. Maternal consequences (GDM, GHT) of participants in Quant's and the present were around 20 percent. Subjects

TABLE 1. Demographic character of singleton pregnancy with normal (n=118) and abnormal (n=14) placental volume.

	Placental volume			*p*-value
	Total	Abnormal	Normal	
Age (years) **	28.6 ± 5.9	32.6 ± 4.9	28.1 ± 5.8	*0.005*
Nulliparity *	43 (32.6)	1 (7.1)	42 (35.6)	*0.032*
Term at birth *	120 (90.9)	13 (92.9)	107 (90.7)	*0.316*
Normal delivery *	85 (64.4)	5 (35.7)	80 (67.8)	*0.018*
EBL (ml) **	317.8 ± 186	421.4 ± 184.7	305.5 ± 183	*0.027*
Normal TWG *	54 (40.9)	5 (35.7)	49 (41.5)	*0.676*
PrP BMI *				*0.059*
Underweight	23 (17.4)	0 (0)	23 (19.5)	
Normal	62 (47)	7 (50)	55 (46.6)	
Overweight	33 (25)	4 (28.6)	29 (24.6)	
Obesity	14 (10.6)	3 (21.4)	11 (9.3)	
MC *				*0.056*
No	102 (77.3)	8 (57.2)	94 (79.7)	
GDM	20 (15.2)	3 (21.4)	17 (14.4)	
GHT	8 (6.1)	3 (21.4)	5 (4.2)	
Others	2 (1.5)	0 (0)	2 (1.7)	
NICU *	7 (5.3)	1 (7.1)	6 (5.1)	*0.745*
Low Apgar *				
1 min	4 (3)	2 (14.3)	2 (1.7)	*0.009*
5 min	1 (0.8)	1 (7.1)	0 (0)	*0.004*
RDS *	6 (4.5)	5 (35.7)	1 (0.8)	*<0.001*
FGR *	7 (5.3)	1 (7.1)	6 (5.1)	*0.745*
Oligo *	10 (7.6)	1 (7.1)	9 (7.6)	*0.948*

*: n (%), **: mean ± standard deviation

Abbreviations: GA: gestational age, EBL: estimated blood loss, TWG: total weight gain, PrP BMI: pre-pregnancy body mass index (kg/m^2), Underweight: BMI < 18.5 kg/m^2, Normal: BMI 18.5–24.9 kg/m^2, Overweight: BMI 25-29.9 kg/m^2, Obesity: BMI ≥30 kg/m^2), MC: maternal consequence, GDM: gestational diabetes mellitus, GHT: gestational hypertension, Others: infectious disease, NICU: neonatal intensive care unit, RDS: respiratory distress syndrome, FGR: fetal growth restriction, Oligo: oligohydramnios

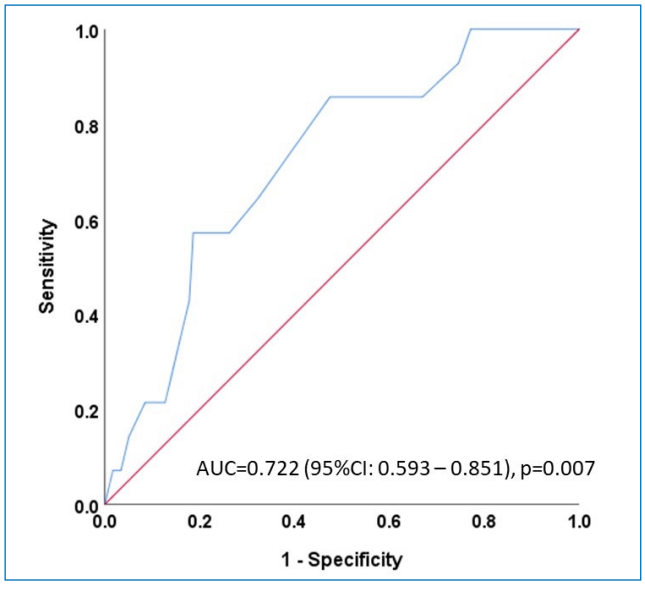


Fig 3. Receiver operating characteristic (ROC) curve of maternal age for prediction of abnormal placental volume (PV).
Abbreviations: AUC: area under curve, CI: confidence interval

TABLE 2. Univariate and multivariate logistic regression for placenta volume abnormality.

	Univariate		Multivariate	
	OR (95%CI)	*p*-value	OR (95%CI)	*p*-value
Ages				
< 34	Ref	*1*		
≥ 34	5.82 (1.83, 18.48)	*0.003*	5.96 (1.35, 26.36)	*0.019*
Gravida				
Primi	Ref	*1*		
Multi	7.18 (0.91, 56.85)	*0.062*		
GA at birth (weeks)				
≥ 37	Ref	*1*		
< 37	1.34 (0.16, 11.21)	*0.789*		
Route				
Vagina	Ref	*1*		
Cesarean	3.79 (1.19, 12.08)	*0.024*	4.31 (0.74, 25.16)	*0.104*
EBL (ml)				
< 500	Ref			
≥ 500	3.46 (1.09,11.04)	*0.036*	1.15 (0.2, 6.67)	*0.878*
Oligo	0.93 (0.11, 7.95)	*0.948*		
TWG				
Normal	Ref	*1*		
Abnormal	1.28 (0.4, 4.05)	*0.676*		
PrP BMI				
Normal	Ref	*1*		
Overweight	1.08 (0.29, 4.01)	*0.904*		
Obesity	2.14 (0.48, 9.6)	*0.319*		
MC				
No	Ref	*1*		
GDM	2.07 (0.5, 8.61)	*0.315*	1.94 (0.35, 10.75)	*0.45*
GHT	7.05 (1.42, 35.03)	*0.017*	1.26 (0.07, 23.81)	*0.877*
FGR	1.44 (0.16, 12.88)	*0.746*		
NICU	1.44 (0.16, 12.88)	*0.746*		
Low Apgar 1 min	9.67 (1.25, 74.95)	*0.03*	0 (0, 1.1)	*0.999*
RDS	65 (6.84, 617.65)	*<0.001*	1.01 (0, 1.1)	*0.999*

Abbreviations: OR: odd ratio, GA: gestational age. EBL: estimated blood loss, Oligo: oligohydramnios, TWG: total weight gain, PrP BMI: pre-pregnancy body mass index (kg/m^2), Underweight: BMI < 18.5 kg/m^2, Normal: BMI 18.5–24.9 kg/m^2, Overweight: BMI 25-29.9 kg/m^2, Obesity: BMI ≥30 kg/m^2, MC: maternal consequence, GDM: gestational diabetes mellitus, GHT: gestational hypertension, Others: infectious disease, FGR: fetal growth restriction, NICU: neonatal intensive care unit, RDS: respiratory distress syndrome

TABLE 3. Comparison adverse pregnancy outcome related to placental volume measuring by 3DUS from various studies

Authors	Present	Schwartz	Reijnders	Soongsatitanon	González	Quant	Farina
Years	2024	2022	2021	2019	2017	2016	2016
Country	Thailand	USA	Netherlands	Thailand	Spain	USA	Italy
Cases (n)	132	422	214	360	988	373	5019
Nulliparity	32.6	17.9	53.7	63.1	63.7	35.8	52.3
GA (weeks)	28-36	11-14	7-11	11-14	11-14	18-24	11-14
Age (years)*	28.6	30.5	32.1	32.8	30.4	31	30.6
BMI (kg/m^2) *	23.4	26.7	24.9	21.5	26.4	22.9	
MC							
No	77.3						
GDM	15.2	2.3			1.6		
GHT	6.1	6.3	4.2		2.6	21.6	
Others	1.4		25.7***				
Prediction	AE	SGA	AE	PrE, FGR	FGR	PrE, SGA	SGA
AE**							
NICU	5.3						
LA1min	3			1.4			
LA5min	0.8			1.1	8.79*		
RDS	4.5			1.1			
FGR	5.3	12.5	7.0	4.7	19.5	10.7	6.23
Preterm	9.1		10.7	35.3	271.5		
PrE**			3.3	2.8		7.2	
Oligo**	7.6						
C/S**	35.6			58.8	21.8		
EBL (ml)*	317.8						

*mean, **n (%), ***Any placental-related complications

Abbreviations: GA: gestational age, 2D: two dimension, 3D: three dimension, GA: gestational age, BMI: body mass index (kg/m2), MC: maternal consequence, Others: infectious disease and others specified as any placenta-related complication, GDM: gestational diabetes mellitus, GHT: gestational hypertension, AE: adverse neonatal event, PrE: preeclampsia, NICU: neonatal intensive care unit, LA1min: low Apgar <7 at 1 min, LA5min: low Apgar <7 at 5 min, RDS: respiratory distress syndrome, FGR: fetal growth restriction, Oligo: Oligohydramnios, C/S: cesarean delivery, EBL: estimate blood loss (ml)

in Reijnders from the Netherlands reported other placental-related pregnancy complications and hypertension were 25.7 and 4.2 percent, respectively. Participants in the current study, Reijnders, and Quant showed 20 percent of complications that affected placental vasculatures. These diseases, namely DM and HT, diminish blood supply to the placenta, leading to decrease in placental size.[20] Low placental volume was strongly correlated to FGR.[1,5,10,11]

Results of the current study supported reports from Schwartz, Reijnders, Soongsatitanon, González, Quant and Farina that small placental volume could be used to predict for small gestational age (SGA) at delivery.[21] Additionally, the study of Soongsatitanon had reported the low placental volume correlated with low Apgar scores at 1 and 5 minutes and neonatal respiratory complications. From the current study, the placental size

which consisted of abnormal placental volumes (<10th percentile of normal range) could be used to predict adverse events (AE), namely FGR, NICU admission, low Apgar scores at 1 and 5 minutes, and obstetric complications (route of delivery and blood loss). We supported that small placental volumes could be used to predict AE, neonatal respiratory, and obstetric complications.

The present study found that the placental volume measurement using 3DUS in the third trimester was a reliable predictor of neonatal birth weight and neonatal outcomes such as low Apgar and respiratory complications. Compared to previous works of Reijnders, Soongsatitanon, and Quant that were conducted during the first and second trimesters, small placental volume was found in which trimester could be used to predict only SGA or preeclampsia. Nevertheless, there were no preeclampsia cases among all participants in our investigation. The reason might be an effect of the prophylaxis prescription of preeclampsia (low-dose aspirin) given to all our participants.[22] The absence of preeclampsia cases led to the inability of the current study to suggest preeclampsia prediction.

In Conclusion, placental volume measurement by 3DUS during the third trimester could be used to predict low Apgar scores and neonatal respiratory complications at delivery period. Abnormal placental volume (<10th percentile of normal range) might be the important warning for obstetricians and pediatricians to be awareness of neonatal complications (birth asphyxia and RDS).

3DUS measurements in the third trimester by experienced MFM fellows and obstetric staff were the strength of this study. The loss of participants to follow up and insufficient equipment were unavoidable and possible limitations of this study. However, placental volume measurement might be interfered by placental site and fetal position. This might be another limitation of the current study. We recommend to perform additional placental volume measurements (3DUS) during the third trimester in all subjects, especially participants who are more than 34 years old for predicting and preparing the possibly adverse events at the time of delivery.

CONCLUSION

Placental volume abnormality increased risk of low Apgar score (OR 9.7) and neonatal respiratory complication (OR 65). Maternal age over 34 years old was associated with placental volume abnormality.

What is already known on this topic?

The placenta is a vital organ for intrauterine development of the fetus. Placental growth and development are typically represented by its weight and volume. Abnormal PV has been linked to obstetric, neonatal and intrapartum complications. Traditionally placental volume is measured using 2DUS during the first and second trimesters of pregnancy. However, with the introduction of 3DUS technology and advanced calculation software, this method has been significantly improved. The shift from 2DUS to 3DUS in measuring placental volume represents a significant advancement in prenatal care.

What does this study add?

Placental volume measurement by 3DUS in the third trimester could predict RDS and birth asphyxia. We recommended the placental volume measurement by 3DUS, especially in parturients older than 34 in the third trimester.

ACKNOWLEDGEMENTS

The present study was funded and supported by Bhumibol Adulyadej Hospital Research Fund. The authors would like to thank all subjects who participated in this study. Special thanks to Sawanya Benchahong, M.D. and Assoc Prof. Densak Pongrojpaw, M.D. for expert consultation.

Conflict of Interest

The author declares no conflict of interest.

Institutional Review Board Statement

This retrospective review has been approved by the local Institutional Review board (reference number: 72/66).

Informed Consent Statement

Permission of all figures was obtained from the patients.

Author Contributions

P.T. conceived of the presented idea and developed the material and methods. K.S. ensured and verified the analytical methods. P.T. and S.M. wrote the manuscript with support from K.B. to investigate formal writing language. N.O. supervised the findings of this work. All authors discussed the results and contributed to the final manuscript.

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